PATENT SPECIFICATION

1,107,510

NO DRAWINGS

1,107,510

Inventors: TSUNG-YING SHEN, WILLIAM VANCE RUYLE and CONRAD PETER DORN, Jr.

Date of Application and filing Complete Specification: 8 June, 1965.
No. 39723/67.
Application made in United States of America (No. 375,307) on 15 June, 1964.
Application made in United States of America (No. 455,360) on 13 May, 1965.
(Divided out of No. 1,107,093.)
Complete Specification Published: 27 March, 1968.

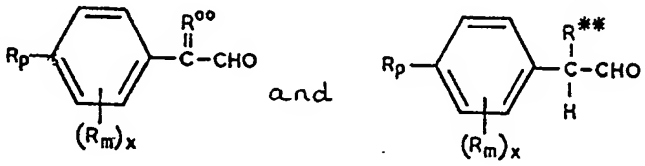
Index at

Int. Cl.:–

ERRATA

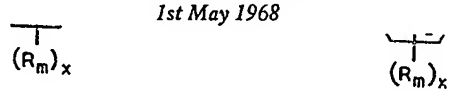
SPECIFICATION No. 1,107,510

Page 1, *for* "formula drawing" *read*

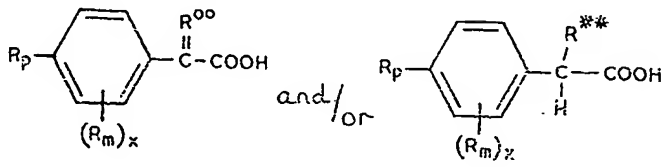


Page 3, line 25, *for* "vacuo" *read "vacuo"*
Page 4, line 54, *for* "acetadehyde" *read* "acetaldehyde"

THE PATENT OFFICE
1st May 1968



in which R°° is a methylene or ethylidene radical, R** is a C_{1-5} alkyl radical, R_p is a cyclohexyl, cyclopentyl or C_{1-5} alkyl radical, R_m is a halogen atom or a C_{1-5} alkoxy, trihalomethyl, C_{1-5} alkylthio, mercapto, amino, di(C_{1-5} alkyl)amino, cyano, nitro, carboxamido, C_{1-6} alkanoylamino, C_{1-4} alkylsulfonyl, di(C_{1-5} alkyl)sulfamoyl or hydroxy radical, x is 1 or 2, but with the provisos that at least one R_m substituent is in the 3- or 5- position and that there is not more than one trihalomethyl substituent in the benzene ring and any such substituent is in the 3- position. There are also claimed methods of preparing such compounds. The present invention provides aldehydes of formulae:



[*Price 4s. 6d.*]

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Complete Specification Published: 27 March, 1968.

Index at acceptance:—C2 C(1E1K3, 1E2K3, 1E2K6, 1E2K7, 1E4K3, 1E4K6, 1E4K7, 1F2C1, 1F2C4, 1F2D2, 1F3C1, 1F3C4, 1F3D2, 1Q4, 1Q6B1, 1Q7A, 1Q8A, 1Q9B, 1Q9F1, 1Q11G, 1Q11J, 2B28, 2B30, 3C6)

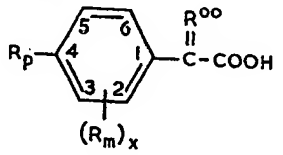
Int. Cl.:—C 07 c 43/30, C 07 c 47/48, C 07 c 79/36, C 07 c 95/08

COMPLETE SPECIFICATION

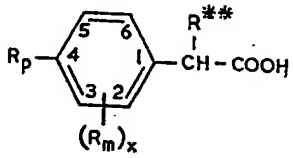
Substituted Araliphatic Aldehydes and their Acetals

We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

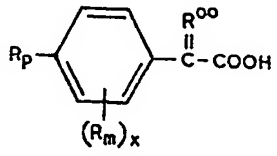
In the specification of our copending application (Serial No. 1107093) No. 24211/65 there are claimed compounds of formulae:



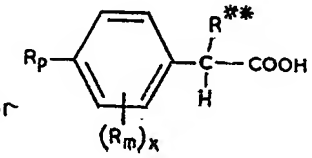
and



in which R^{∞} is a methylene or ethylidene radical, R^{**} is a C_{1-5} alkyl radical, R_p is a cyclohexyl, cyclopentyl or C_{1-5} alkyl radical, R_m is a halogen atom or a C_{1-5} alkoxy, trihalomethyl, C_{1-5} alkylthio, mercapto, amino, di(C_{1-5} alkyl)amino, cyano, nitro, carboxamido, C_{1-6} alkanoylamino, C_{1-4} alkylsulfonyl, di(C_{1-5} alkyl)sulfamoyl or hydroxy radical, x is 1 or 2, but with the provisos that at least one R_m substituent is in the 3- or 5- position and that there is not more than one trihalomethyl substituent in the benzene ring and any such substituent is in the 3- position. There are also claimed methods of preparing such compounds. The present invention provides aldehydes of formulae:



and/or



SEE ERRATA SLIP ATTACHED

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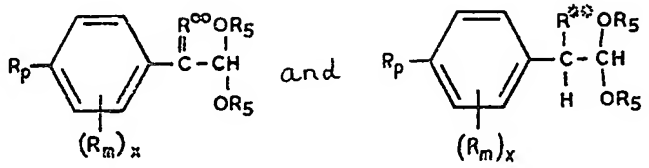
and acetals of formulae:



where R_m, R_p, R**, R°° and x are as defined above and R_s is an alkyl radical. Preferably, the substituent on the alpha-carbon atom (i.e. R°° or R**) is methyl or methylene and R_p is cyclohexyl.

The development of antiinflammatory compounds in the past two decades has seen the growth of a great many new drugs. Most of these have been steroids of the 11-oxygenated pregnane series. These, while highly effective, have the drawback of causing many side effects. There is a need in the market for equally effective compounds of much simpler structure and having less side effects.

It has been found that compounds of this invention are potent antiinflammatory agents. They are effective in the prevention and inhibition of granuloma tissue formation. Certain of them possess this activity in high degree and are of value in the treatment of arthritic and dermatological disorders and in like conditions which are responsive to treatment with antiinflammatory agents. In addition, the compounds of this invention have a useful degree of antipyretic and analgesic activity and also indicate some fatty acid synthesis inhibition. For these purposes, they are administered in pharmaceutical compositions, normally orally, e.g. in tablets or capsules, the optimum dosage depending, of course, on the particular compound being used and the type and severity of the condition being treated. Although the optimum quantities of these compounds of this invention to be used in such manner will depend on the compound employed and the particular type of disease condition treated, oral dose levels of preferred compounds in the range of 1.0—2,000 mg. per day are useful in control of arthritic conditions, depending on the activity of the specific compound and the reaction sensitivity of the patient.

Certain of the compounds of the present invention possess asymmetric carbon atoms and are ordinarily present in the form of a racemic mixture.

The novel aldehyde compounds are prepared from halides of the corresponding carboxylic acids by reducing the compound by means known to be capable of effecting such reduction (i.e., in use or described in the literature as suitable for this purpose). The reduction is preferably effected by first protecting any hydroxy or primary amino group present at R_m in the acid itself, reacting the acid with a halogenating agent, e.g. thionyl chloride, thionyl bromide, phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride or phosphorus oxybromide, but preferably thionyl chloride, in an inert solvent such as benzene, toluene, xylene, ethers (e.g. diethyl ether or dioxane), or tetrahydrofuran, preferably benzene or toluene at any suitable temperature (room temperature to reflux, preferably at or near the reflux temperature of the system) until the fomation of the acid halide is substantially complete, and reacting the acid halide with a Rosenmund catalyst such as 5% palladium on barium sulphate with quinoline or preferably with a tritertiarybutoxy alkali or alkaline-earth metal aluminium hydride such as potassium, sodium, or lithium aluminium hydride, in an inert solvent such as benzene, toluene, xylene, an ether (e.g. diethyl ether or dioxane) or tetrahydrofuran, preferably tetrahydrofuran or diethyl ether, at any suitable temperature (−80°C to room temperature), preferably −35° to −15°C., until the reaction is substantially complete.

It is preferred to remove the hydrohalic acid and sulphur dioxide formed after the acid halide preparation; otherwise, the inorganic acid would preferentially consume the subsequent addition of the hydride. However, if it is desired, the inorganic acid may remain if an excess of the hydride is used to react with the inorganic acid as well as the acid halide. The preferred hydride in this step is the tritertiarybutoxy lithium aluminium hydride. When this reagent is used, it is preferred to use temperatures below 0°C. At temperatures above 0°C, the reduction will preferentially lead to the corresponding alcohol instead of the aldehyde, so that the reaction is not then economically feasible.

Any hydroxy and primary amino groups present in the acid as R_m are preferably

protected by benzylation before the acid is converted to its acid halide. The benzyl groups will be removed during the subsequent reduction reaction.

The acetals are prepared from the aldehydes by reaction with an alkanol in the presence of an acid catalyst, preferably a strong acid such as *p*-toluenesulphonic acid, *p*-nitrobenzenesulphonic acid, benzenesulphonic acid, trichloroacetic acid, or a mineral acid (e.g. hydrochloric acid, hydrobromic acid and sulphuric acid), or boron trifluoride. It is preferred to carry out the reaction with a catalytic amount of *p*-toluenesulphonic acid or concentrated hydrochloric acid and with a C_{1-6} alkanol (e.g. methanol, ethanol, propanol or butanol, preferably methanol) using an excess of the alcohol or a combination of the alcohol with an ether or aromatic compound as solvent at any suitable temperature (0°C to reflux, preferably ambient temperatures) until the reaction is substantially complete.

The quantity of acid is not critical as long as the acid used is one strong enough to catalyse the reaction. This reaction may also be carried out using the aldehyde and the appropriate lower alkyl orthoformate. When it is desired to isolate the acetal formed in this step and water is to be used in the isolation procedure, the reaction mixture must be neutralized with a compound such as sodium carbonate so as to prevent the hydrolysis of the acetal back to the aldehyde.

The following examples illustrate the invention:

EXAMPLE 1

Alpha-methyl-3-chloro-4-cyclohexylphenyl acetaldehyde

A. Alpha-methyl-3-chloro-4-cyclohexylphenyl acetyl chloride

To a solution of 0.01 mole of alpha-methyl-3-chloro-4-cyclohexylphenyl acetic acid in 50 cc. of benzene is added 0.011 mole of thionyl chloride. The solution is heated on the steam bath for 1 hour and then concentrated *in* vacuo to remove the solvent and any excess thionyl chloride. 25 ml. of benzene is then added and removed *in vacuo* to yield alpha-methyl-3-chloro-4-cyclohexylphenyl acetyl chloride.

B. Alpha-methyl-3-chloro-4-cyclohexylphenyl acetaldehyde

To a suspension of 0.01 mole tritertiarybutoxy lithium aluminium hydride in 50 cc. dry tetrahydrofuran is added dropwise with stirring a solution of 0.01 mole of alpha-methyl-3-chloro-4-cyclohexylphenyl acetyl chloride in 25 cc. dry tetrahydrofuran. The reaction mixture is stirred at −10°C for 3 hours followed by the addition of 200 cc. of 5% sulphuric acid added cautiously, and the resultant mixture extracted well with (3 × 75 ml.) ether. The combined ether extracts are washed with water, dried over sodium sulphate, and concentrated. The residue is chromatographed on 250 grams of silica gel and eluted with 10—90% ether-petroleum ether to yield alpha-methyl-3-chloro-4-cyclohexylphenyl acetaldehyde.

When alpha-methyl-3-bromo-4-cyclohexylphenyl acetic acid, alpha-methyl-3-chloro-4-cyclopentylphenyl acetic acid, alpha-methyl-3-chloro-4-secondarybutylphenyl acetic acid, alpha-methyl-4-cyclohexyl-2,5-dichlorophenyl acetic acid, alpha-methyl-2-bromo-5-chloro-4-cyclohexylphenyl acetic acid, alpha-methyl-5-bromo-2-chloro-4-cyclohexylphenyl acetic acid, alpha-methyl-4-cyclohexyl-3-trifluoromethylphenyl acetic acid, alpha-methyl-4-cyclohexyl-2,3-dichlorophenyl acetic acid, alpha-methyl-4-cyclohexyl-3,5-dichlorophenyl acetic acid, alpha-ethyl-3-chloro-4-cyclohexylphenyl acetic acid, alpha-ethyl-4-cyclohexyl-3-trifluoromethylphenyl acetic acid, alpha-methyl-4-cyclohexyl-3-nitrophenyl acetic acid, alpha-methyl-5-chloro-4-cyclohexyl-2-nitrophenyl acetic acid, alpha-methyl-2-amino-5-chloro-4-cyclohexylphenyl acetic acid, alpha-methyl-4-cyclohexyl-3-methylsulphonylphenyl acetic acid, and alpha-methyl-3-substituted, 2-, 5-, and 6-substituted-4-cyclohexylphenyl acetic acid compounds, alpha-methyl-2-, 5- and 6-aminophenyl acetic acid compounds, alpha-methyl-2-, 5- and 6-hydroxyphenyl acetic acid compounds and alpha-methyl-2-, 5- and 6-fluorophenyl acetic acid compounds obtained from Example 2 of the specification of our copending application No. 24211/65 (except those compounds containing a nitro group) are used in place of alpha-methyl-3-chloro-4-cyclohexylphenyl acetic acid in Part A of the above example and the product thereof used in Part B of the above example, there are obtained alpha-methyl-3-bromo-4-cyclohexylphenyl acetaldehyde, alpha-methyl-3-chloro-4-cyclopentylphenyl acetaldehyde, alpha-methyl-3-chloro-4-secondarybutylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-2,5-dichlorophenyl acetaldehyde, alpha-methyl-2-bromo-5-chloro-4-cyclohexylphenyl acetaldehyde, alpha-methyl-5-bromo-2-chloro-4-cyclohexylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3-trifluoromethylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-2,3-dichlorophenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3,5-dichlorophenyl acetaldehyde, alpha-ethyl-3-

chloro-4-cyclohexylphenyl acetaldehyde, alpha-ethyl-4-cyclohexyl-3-trifluoromethylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3-nitrophenyl acetaldehyde, alpha-methyl-5-chloro-4-cyclohexyl-2-nitrophenyl acetaldehyde, alpha-methyl-2-amino-5-chloro-4-cyclohexylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3-methylsulphonylphenylacetaldehyde, and alpha-methyl-3-substituted, 2-, 5- and 6-substituted-4-cyclohexylphenyl acetaldehyde compounds, alpha-methyl-2, 5- and 6-aminophenyl acetaldehyde compounds, alpha-methyl-2-, 5- and 6-hydroxyphenyl acetaldehyde compounds and alpha-methyl-2-, 5- and 6-fluorophenyl acetaldehyde compounds (except those compounds containing a nitro group) respectively.

EXAMPLE 2

Alpha-methyl-3-chloro-4-cyclohexylphenyl acetaldehyde dimethyl acetal

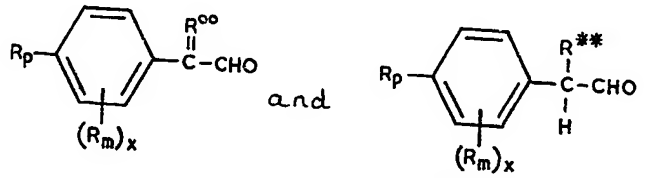
To a solution of 0.01 mole of alpha-methyl-3-chloro-4-cyclo-hexylphenyl acetaldehyde in 100 cc. of anhydrous methanol is added 0.001 mole of *p*-toluenesulphonic acid. The reaction mixture is stirred at room temperature for 5 days. A solution of sodium methoxide in methanol is added until the solution is just alkaline to moistened litmus paper. The methanol is removed *in vacuo* and the residue taken up in ether and washed well with water. The ether solution is dried over sodium sulphate and concentrated. The residue is chromatographed on neutral alumina. Elution with ether-petroleum ether (10—90%) gives the dimethyl acetal of alpha-methyl-3-chloro-4-cyclohexylphenyl acetaldehyde.

When ethanol, *n*-propanol, and *n*-butanol are used in place of methanol in the above example, there are obtained the corresponding diethyl, dipropyl and dibutyl acetals.

When alpha-methyl-3-bromo-4-cyclohexylphenyl acetaldehyde, alpha-methyl-3-chloro-4-cyclopentylphenyl acetaldehyde, alpha-methyl-3-chloro-4-secondarybutylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-2,5-dichlorophenyl acetaldehyde, alpha-methyl-2-bromo-5-chloro-4-cyclohexylphenyl acetaldehyde, alpha-methyl-5-bromo-2-chloro-4-cyclohexylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3-trifluoromethylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-2,3-dichlorophenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3,5-dichlorophenyl acetaldehyde, alpha-ethyl-3-chloro-4-cyclohexylphenyl acetaldehyde, alpha-ethyl-4-cyclohexyl-3-trifluoromethylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3-nitrophenyl acetaldehyde, alpha-methyl-5-chloro-4-cyclohexyl-2-nitrophenyl acetaldehyde, alpha-methyl-2-amino-5-chloro-4-cyclohexylphenyl acetaldehyde, alpha-methyl-4-cyclohexyl-3-methylsulphonylphenyl acetaldehyde, and alpha-methyl-3-substituted, 2-, 5- and 6-substituted-4-cyclohexylphenyl acetaldehyde compounds, alpha-methyl-2-, 5- and 6-aminophenyl acetaldehyde compounds, alpha-methyl-2-, 5- and 6-hydroxyphenyl acetaldehyde compounds and alpha-methyl-2-, 5- and 6- fluorophenyl acetaldehyde compounds obtained from Example 1 are used in place of alpha-methyl-3-chloro-4-cyclohexylphenyl acetaldehyde in the above example, there are obtained alpha-methyl-3-bromo-4-cyclohexylphenyl acetaldehyde dimethyl acetal, alpha-methyl-3-chloro-4-cyclopentylphenyl acetaldehyde dimethyl acetal, alpha-methyl-3-chloro-4-secondarybutylphenyl acetaldehyde dimethyl acetal, alpha-methyl-4-cyclohexyl-2,5-dichlorophenyl acetaldehyde dimethyl acetal, alpha-methyl-2-bromo-5-chloro-4-cyclohexylphenyl acetaldehyde dimethyl acetal, alpha-methyl-5-bromo-2-chloro-4-cyclohexylphenyl acetaldehyde dimethyl acetal, alpha-methyl-4-cyclohexyl-3-trifluoromethylphenyl acetaldehyde dimethyl acetal, alpha-methyl-4-cyclohexyl-2,3-dichlorophenyl acetaldehyde dimethyl acetal, alpha-methyl-4-cyclohexyl-3,5-dichlorophenyl acetaldehyde dimethyl acetal, alpha-ethyl-3-chloro-4-cyclohexylphenyl acetaldehyde dimethyl acetal, alpha-ethyl-4-cyclohexyl-3-trifluoromethylphenyl acetaldehyde dimethyl acetal, alpha-methyl-4-cyclohexyl-3-nitrophenyl acetaldehyde dimethyl acetal, alpha-methyl-5-chloro-4-cyclohexyl-2-nitrophenyl acetaldehyde dimethyl acetal, alpha-methyl-2-amino-5-chloro-4-cyclohexylphenyl acetaldehyde dimethyl acetal, alpha-methyl-4-cyclohexyl-3-methylsulphonylphenyl acetadehyde dimethyl acetal, and alpha-methyl-3-substituted, 2-, 5- and 6-substituted-4-cyclohexylphenyl acetaldehyde dimethyl acetal compounds, alpha-methyl-2-, 5- and 6-aminophenyl acetaldehyde dimethyl acetal compounds, alpha-methyl-2-, 5- and 6-hydroxyphenyl acetaldehyde dimethyl acetal compounds and alpha-methyl-2-, 5- and 6-fluorophenyl acetaldehyde dimethyl acetal compounds, respectively.

WHAT WE CLAIM IS:

1. Aldehydes of general formulae:

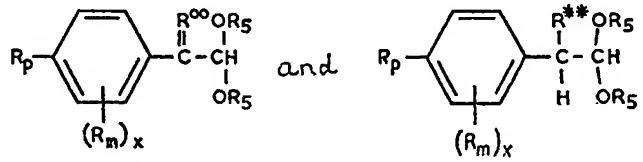


in which R^{oo} is a methylene or ethylidene radical, R^{**} is a C_{1-5} alkyl radical, R_p is a cyclohexyl, cyclopentyl or C_{1-5} alkyl radical, R_m is a halogen atom or a C_{1-5} alkoxy, trihalomethyl, C_{1-5} alkylthio, mercapto, amino, di(C_{1-5} alkyl)amino, cyano, nitro, carboxamido, C_{1-6} alkanoylamino, C_{1-4} alkylsulphonyl, di(C_{1-5} alkyl)sulphamoyl or hydroxy radical, and x is 1 or 2, but with the provisos that at least one R_m substituent is in the 3- or 5- position and that there is not more than one trihalomethyl substituent in the benzene ring and any such substituent is in the 3- position.

2. A compound as claimed in claim 1, in which the alpha-carbon has a methylene or methyl substituent attached to it and R_p is cyclohexyl.

3. Each and every compound as claimed in claim 1, hereinbefore individually specified.

4. Acetals of general formulae:

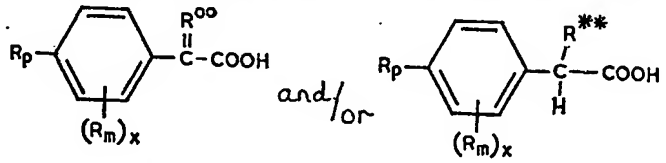


in which R_p, R_m, R^{oo}, R^{**} and x are as defined in claim 1 and R_5 is an alkyl radical.

5. A compound as claimed in claim 4, in which the alpha-carbon has a methyl or methylene substituent attached to it, R_p is cyclohexyl, and R_5 is methyl.

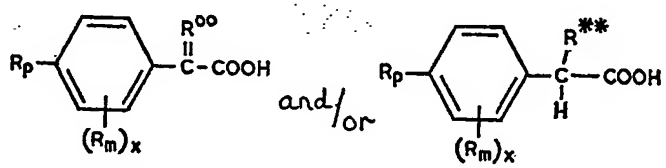
6. Each and every compound as claimed in claim 4, hereinbefore individually specified.

7. The process that comprises reducing a halide of an acid of general formula:



where R_p, R_m, R^{oo}, R^{**} and x are as defined in claim 1, by means known to be capable of reducing a carboxylic acid halide to the corresponding aldehyde to produce a compound as claimed in claim 1.

8. The process that comprises protecting any hydroxy or primary amino groups in an acid of general formula:



where R_p, R_m, R^{oo}, R^{**} and x are as defined in claim 1, converting the acid to an acid halide by reaction with a halogenating agent, and reducing the resulting halide with a Rosenmund catalyst or with an alkali-metal or alkaline-earth metal aluminium hydride to produce a compound as claimed in claim 1.

9. A process as claimed in claim 8, in which the halogenating agent is thionyl chloride and the reduction is effected with lithium aluminium hydride in tetrahydrofuran or diethyl ether at below 0°C.

10. A process as claimed in claim 8 or 9 in which the hydroxy or primary amine groups, if any, are protected by benzylation.

11. A process as claimed in any one of claims 7—10, in which the reduction is carried out at −35 to −15°C.

12. A process as claimed in claim 7, substantially as hereinbefore described in Example 1.

13. A process as claimed in any one of claims 7—12, including the step of preparing the starting material by a process claimed in the specification of our co-pending application No. 24211/65.

14. The process that comprises reacting a compound as claimed in claim 1 with an alkanol in the presence of an acid catalyst to produce a compound as claimed in claim 4.

15. A process as claimed in claim 14, in which the alkanol is methanol and the acid is *p*-toluenesulphonic acid or concentrated hydrochloric acid.

16. A process as claimed in claim 14, substantially as hereinbefore described in Example 2.

17. A process as claimed in any one of claims 14—16, including the step of preparing the starting material by a process as claimed in any one of claims 7—12.

18. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 7—13 or its obvious chemical equivalent.

19. A compound as claimed in claim 4, when prepared by a process as claimed in any one of claims 14—17 or its obvious chemical equivalent.

20. A pharmaceutical composition containing as active ingredient a compound as claimed in any one of claims 1—6, 18 and 19.

21. A composition as claimed in claim 20, in the form of a tablet or capsule.

For the Applicants:
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